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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/630,215	08/01/2000	John F. O'Connor	54205-A-PCT-US/JPW/SHS/MV	7218

7590 11/17/2004

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/630,215	O'CONNOR ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11/04/04*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Response

1. Applicant's response filed 10/14/04 is acknowledged. Claims 58-67 are pending and remain under examination.

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 58-67 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 53, 59, 60, 65, 71, 72, and 77-82 of copending Application No. 09/017, 976, now US Patent 6,500,627, for reasons of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claim 62 and 67 is rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Cole et al. (US Patent 6,429,018) for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al. (US Patent 6,429,018) in view of Birken et al. (Endocrinology, 1993) for reasons of record.

5. Claims 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cole et al. (US Patent 6,429,018) in view of Birken et al. (Endocrinology, 1993) and in further view of Foster et al. (US Patent 4,444,879) for reasons of record.

Response to Arguments

6. Applicant's arguments filed 10/14/04 have been fully considered but they are not persuasive.

A) Applicant argues that Examiner has given the term "hyperglycosylated isoform of gonadotropin" an interpretation broader than, and inconsistent with the definition taught by Cole because Cole limits its definition to "hyperglycosylated gonadotropin, nicked gonadotropin, etc. which exhibit aberrant carbohydrate profiles and/or levels as compared to normal. Applicant specifically contends that Cole does not define a hyperglycosylated gonadotropin to include hCG isoforms present during the early pregnancy of a subject; i.e. EPMI-hCG, as recited in the instant claims.

Contrary to Applicant's argument, Cole, indeed, defines a hyperglycosylated gonadotropin to include hCG isoforms expressed during early pregnancy of a subject in column 5, lines 14-18 and column 7, lines 21-39 wherein an advantage of using the method includes an early assay for Down's Syndrome because the screen can be used in the first trimester of pregnancy.

B) Applicant argues that Cole does not teach an antibody which binds to EPMI-hCG that is recognized by B152 antibody deposited with the ATCC No. HB-12467 as taught in claim 67 and that the B152 antibody taught by Cole recognizes at best nicked hCG obtained from choriocarcinoma patients.

In response, the B152 antibody taught by Cole recognizes and binds a hyperglycosylated gonadotropin isoform that is manifested early during pregnancy in Down's syndrome cases, which appears to encompass Applicant's EPMI-hCG. Moreover, there is no objective evidence of record submitted by Applicant, such as side-by-side testing, that establishes that the B152 antibody taught by Cole that recognizes and binds the hyperglycosylated gonadotropin isoform that is manifested early during pregnancy in Down's syndrome cases and Applicant's B152 antibody deposited with the ATCC No. HB-12467 which recognizes and binds to EPMI-hCG, are two distinct antibodies. Alternatively, the Office is in no position to determine experimentally whether or not, in an invention such as at issue, the Applicant's B152 antibody is the same as that of the Cole reference. Accordingly, in such instances, this shifts the burden to the Applicant who has the resources to make such a determination and is in a better position to determine experimentally the difference between the invention as claimed and that of the art. In re Pye, 355 F2d 641, 148 USPQ 426 (CCPA 1966). Accordingly, the rejection of claims 62 and 67 under 35 U.S.C. 102 as being anticipated by Cole is being maintained.

C) Applicant argues that the combination of Cole with Birken fails to support a prima facie case of obviousness and hence, does not render obvious the claimed invention because the cited references do not teach or fairly suggest methods for predicting pregnancy outcome in a subject by determining the ratio of EMI-hCG to intact hCG in a sample. Applicant contends that Cole does not teach the detection of EPMI-

hCG, and Birken also does not teach or suggest EPMI-hCG and only teaches an analytical method for separating intact hCG from hCGB core fragment and B108 and B109 antibodies that recognize intact hCG.

In response, Cole teaches a method for determining an amount of hyperglycosylated gonadotropin manifested during early pregnancy in Down's Syndrome cases using B152 antibody which binds the hyperglycosylated gonadotropin. Urine sample is obtained from a subject in her first trimester, within about the first 9 weeks to 13 weeks of pregnancy. Birken is incorporate therewith, for teaching two-site immunometric assay used to evaluate early pregnancy losses using B108 antibody and B109 antibody in combination with other antibodies. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to further incorporate monoclonal antibodies in the immunometric assay method as taught by Cole with the method taught by Birken because Birken specifically taught that use of two-site immunometric assay that separates hCG forms provides advantage in monitoring different complex hCG functions.

In as far as calculating a ratio between EPMI-hCG and intact hCG, wherein a ratio greater than 1 provides a correlation indicative of positive pregnancy outcome, first of all, it has previously been agreed upon that the cited references are not anticipatory references. It is then respectfully submitted that the instant claimed multivariant analysis of EPMI-hCG and INN-hCG in a two site immunoradiometric assay in order to provide a predictive correlation of positive or negative pregnancy outcome (encompassing Down syndrome cases) is obvious from the cited references. The

combined references clearly teach that the B152 antibody recognizes and binds nicked hyperglycosylated hCG and is used in determining EPMI-hCG as a prenatal screen for Down's Syndrome cases while B109 antibody and B108 antibody recognize and bind INN-hCG and are combined with other antibodies to determine early pregnancy loss. For that reason, assaying a single sample for these analytes using multivariant analysis significantly increases both the sensitivity and specificity that commands the predictive capacity of the assay in determining a pregnancy outcome. This is precisely the power of multivariant analysis. Accordingly, it is maintained that determining the ratio of EPMI-hCG to INN-hCG in a single sample as being "greater than 1" amounts to obtaining a result effective variable which the prior art references have shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitation recited in instant claim 58 is for any other particular purpose than that which is obvious, and the prior art suggests that in multivariant analysis, ratios often vary according to the different analytes being analyzed, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable range of the methods disclosed by the prior art by normal optimization procedure.

D) Applicant argues that the combination of Foster with Cole and Birken does not render obvious claims 63-66 of the instant invention because Foster only teaches incorporating labels, antibodies, and reagent into a kit format but does not teach or suggest using EPMI-hCG in a kit format.

In response to applicant's argument against Foster individually as failing to teach using EPMI-hCG in a kit format, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the rejection was based on the combined teaching of Cole, Birken, and Foster to arrive at the claimed invention. Cole and Birken are discussed supra. Foster is incorporated with the teaching of Cole and Birken only for the teaching of incorporating labels, antibodies, and reagents into a kit format. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the antibodies, solid support, and labels taught by Cole and Birken into a kit arrangement as taught by Foster because test kits are conventional and well known in the art for their recognized advantages of convenience and economy.

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
November 4, 2004

Christopher L. Chin

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11/6/04